

The optimal neoadjuvant chemotherapy regime for muscle-invasive bladder cancer: still an open question?

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Recently the phase III randomized clinical trial (VESPER) by Pfister et al. [1] was published. This was an awaited randomized study of neoadjuvant (NAC) or adjuvant (AC) chemotherapy comparing 6 cycles of experimental 2-weekly dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) vs. 4 cycles of standard-of-care (SOC) 3-week schedule gemcitabine and cisplatin (GC) for patients with non-metastatic, muscle-invasive bladder cancer (MIBC) planned for subsequent radical cystectomy. The trial did not reach significance for the primary endpoint of 3-year progression free survival (PFS) in the entire population but showed a significantly prolonged 3-year PFS in a prespecified analysis of the NAC-subgroup. Overall survival (OS) data are immature.

The authors should be commended for performing a large, randomized trial which is the first ever finalized in this difficult to treat population. However, we have some concerns before implementing ddMVAC based on the VESPER study as the new gold SOC.

In many centers in the Nordic countries, NAC with the GC regime for MIBC has been a well-established SOC for the last two decades, and we have adhered to strict criteria for initiating treatment. Within NUCOG (Nordic Urothelial Cancer Oncology Group) [2], we recently compared NAC GC 3-week vs. 4-week schedule in a Nordic retrospective trial with more than 700 patients and observed a higher proportion of pathologic complete response (ypCR) for the 3-week schedule, but less toxicity with the 4-week schedule [3]. However, the higher ypCR rate did not translate to better outcome, with similar OS and relapse-free survival (RFS) between the two schedules. We estimate a 3-year RFS of approximately 75% for GC. Although, our study was retrospective, this compares favorably to the observed 3-year PFS of 56% in the SOC arm and 66% in the ddMVAC arm of the VESPER trial. Further, we reported a higher downstaging rate compared to the VESPER trial, with an ypT0 of 46% for the 3-week regimen of GC compared to 36% in the SOC arm and 42% in the ddMVAC arm in the VESPER trial. Curiously, in the VESPER trial a surprisingly high proportion of what can be considered non-responders (pT2–pT4 and/or N+) of 50% was

observed in the SOC arm vs. 36% in the ddMVAC arm. This was most evident with 37% of patients in the SOC arm having $\geq$ ypT3 or ypN1 after NAC and cystectomy. In comparison, for the 3-week GC regimen in our Nordic study, 41% of the patients were considered non-responders of which 28% were $\geq$ ypT3 or ypN1. In the Vesper trial, a baseline CT was performed before NAC. The sensitivity and specificity of CT for detecting lymph nodes preoperatively is low, which may explain the high proportion of cT2N0 patients in that study [4]. European Association of Urology (EAU) guidelines suggests PET/CT as a possible imaging modality for staging [5]; it is possible that if PET/CT would have been used in the VESPER trial, a higher number of cN+ patients would have been detected and offered induction chemotherapy rather than NAC. Moreover, pretreatment clinical stage (cTNM) has been shown to be a significant prognostic factor for pathological downstaging (ypTNM) at cystectomy [6,7]. Notably, in the VESPER trial, in the NAC subgroup >90% had only a cT2-stage (<cT3), which correlate poorly to the baseline characteristics in our Nordic study, and everyday clinical experience. We speculate if there could have been some under-staging at baseline, and thus possibly some imbalance between treatment arms, which could have influenced the findings. This to us highlights the importance and difficulties of accurate clinical and radiological assessment at baseline. These concerns were also expressed by Zeng et al. [8] although the questions have been addressed [9].

The VESPER trial did show a higher proportion of pathologic downstaging to non-muscle invasive bladder cancer of 63% for ddMVAC compared to 50% for GC. In our trial, the 3-weekly GC schedule did seem to perform better, with a 60% obtaining <pT2N0 [3].

A concern with the ddMVAC regimen is the toxicity, with only 60% of patients completing the planned 6 cycles of treatment compared to 84% in the SOC arm.

Current practice in few Nordic centers is to administer 4 cycles of ddMVAC as shown by Choueri et al. [10], however, it is unknown how this compares to 6 cycles of ddMVAC in the VESPER trial.

Increased toxicity was observed in the experimental ddMVAC arm with significantly more patients experiencing anemia, asthenia, and nausea/vomiting. Furthermore, four deaths were observed in the trial of which three occurred in the ddMVAC arm, although it is unclear if these were treatment related. In the trial, comparing conventional MVAC vs. GC in the metastatic setting by Maase et al. the MVAC treatment proved to be very toxic [11], and although the ddMVAC regime may be more tolerable [12], we advise caution before introducing ddMVAC in a standard patient population where patients are likely to be less fit for treatment and with more comorbidities in comparison to a clinical trial cohort [13].

Finally, the question of NAC vs. AC is still ongoing, with the CHECKMATE-274 trial recently showing prolonged disease-free survival of adjuvant Nivolumab, also for the subgroup of patients unable to receive NAC [14].

In summary the PFS data of ddMVAC in the VESPER trial are promising, but we remain cautious as to recommend the optimal NAC regime for a broader patient population, and currently suggest awaiting mature OS data before reaching more definitive conclusions.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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